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Potential restoration of HDL function with apolipoprotein A-I mimetic peptide in end-stage renal disease

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High-density lipoprotein (HDL) cholesterol level is low in dialysis patients. The HDL that is present is dysfunctional, failing to protect low-density lipoprotein (LDL) from oxidation and reduce levels of oxidized LDL. Addition of the orally absorbable amphipathic peptide 4-F to LDL obtained from dialysis patients protects LDL from oxidation *in vitro* and reduces the capacity of oxidized LDL to induce expression of monocyte chemoattractant protein-1 (MCP-1) by vascular endothelial function in culture, potentially providing a tool to reduce cardiovascular risk in dialysis patients.

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For patients with stage V chronic kidney disease (CKD), the risk of cardiovascular disease is increased as much as tenfold beyond that predicted by Framingham risk factors. While there are several processes associated with this increase, including abnormalities in calcium and phosphorous metabolism and inflammation, it is clear that lipoprotein metabolism is disordered.

Increased low-density lipoprotein (LDL) levels are not associated with mortality in this population, but low high-density lipoprotein (HDL) levels are.¹ HDL is normally protective, both because it effects reverse cholesterol transport, stripping cholesterol from endothelial-bound macrophages and returning it to the liver (Figure 1), and because it serves as an anti-inflammatory and antioxidative

protein. However, it has been shown previously that HDL isolated from dialysis patients is less effective in protecting LDL from oxidation as compared with HDL obtained from normal individuals, while at the same time LDL from dialysis patients is more readily oxidized than LDL obtained from normal subjects.² Although LDL cholesterol levels are not a cardiovascular risk factor among dialysis patients, the level of oxidized LDL is. HDL levels are reduced in patients with CKD, and the HDL that is present is dysfunctional.

Efforts to reduce the excessive cardiovascular burdens among patients with stage V CKD by multiple different strategies—using non-phosphorous calcium binders; lowering LDL cholesterol with statins in two large randomized clinical trials; increasing hemoglobin with erythropoietic agents; increasing the dose of dialysis delivered—have thus far not shown benefit. Vaziri *et al.*³ (this issue) used an apolipoprotein (Apo)A-I mimetic peptide in an *in vitro* system and showed that it could reduce the effect of oxidized LDL on stimulation of cultured aortic endothelial cells—even beyond the protection afforded by HDL obtained from normal subjects—to produce the cytokine monocyte chemoattractant protein-1

(MCP-1). This could possibly provide a pharmacologic substitute for the dysfunctional HDL present in CKD.

Decreased HDL cholesterol concentration is a prominent risk factor for the onset of kidney disease, for loss of kidney function once CKD is present,⁴ and for cardiovascular disease both among patients with CKD and among dialysis patients.¹ Although fibric acid derivatives do increase HDL cholesterol level, they do not reduce the risk of progression of renal failure or alter cardiovascular outcome;⁵ this suggests that more HDL per se may not resolve the effects of altered lipoprotein levels in these patients and that HDL structure and function may also play a role.

ApoA-I, the principal apolipoprotein contained in HDL, is synthesized and secreted by the liver and gut. It then engages the adenosine triphosphate-binding cassette transporter A-1 (ABCA1)—or, more specifically, ABCG1, located on endothelial-bound macrophages—acquiring cholesterol and initiating reverse cholesterol transport (Figure 1). The nascent discoidal HDL particle, migrating in the pre- β -HDL range, is then acted upon by lecithin-cholesterol acyltransferase (LCAT), which esterifies cholesterol; this allows the more lipophilic cholesterol esters to sink into the core, forming spherical α -migrating HDL₃ and, by further action of the same enzyme, creating the larger, more buoyant HDL₂. HDL₂ engages scavenger receptor B1 and is thus taken up by the liver, concluding reverse cholesterol transport (Figure 1). LCAT activity decreases with increasing vintage⁶ (years on dialysis) in hemodialysis patients and recovers after kidney transplantation,⁷ suggesting that this defect is conferred by kidney failure. A decrease in LCAT reduces the rate of HDL maturation, favoring a relative increase in both small, dense isoforms of HDL, primarily pre- β -HDL, and, to a lesser extent, HDL₃. In healthy individuals the HDL₃ isoform is a better antioxidant than the larger HDL₂ isoform. HDL₃ carries a greater concentration of the antioxidative enzymes paraoxonase 1 (PON1) and aryl hydrocarbon hydrolase and other anti-inflammatory proteins. PON1 activity is reduced in patients with

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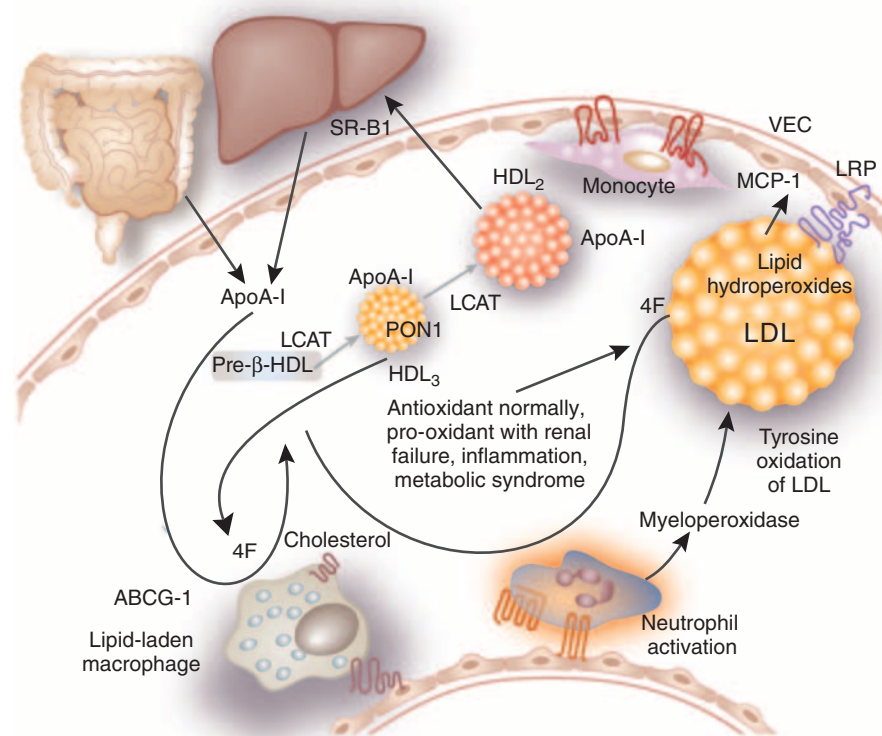


Figure 1 | Maturation of HDL and the protective effect of the ApoA-I mimetic peptide 4F. Apolipoprotein (Apo)A-I is secreted by the liver and gut and engages the adenosine triphosphate-binding cassette transporter G-1 protein (ABCG1), taking up cholesterol from macrophages and forming discoidal pre-β-migrating HDL. HDL is matured by action of lecithin-cholesterol acyltransferase (LCAT), forming HDL₃ and, ultimately, large buoyant HDL₂, which is then taken up by the liver, engaging scavenger receptor B1 (SR-B1). HDL₃ and, to a lesser extent, HDL₂ are normally rich in antioxidative enzymes, including paraoxonase 1 (PON1). Oxidized LDL carries lipid hydroperoxides, binds to vascular endothelium via the lipoprotein-like receptor (LRP), and stimulates vascular endothelial cells (VEC) to produce monocyte chemoattractant protein-1 (MCP-1). The amphipathic 18-amino-acid peptide 4F both retrieves lipid hydroperoxides from LDL and substitutes for ApoA-I in uptake of cholesterol by engaging ABCG1, protecting endothelial cells from inflammation.

CKD in part because of accumulation of advanced glycation end products and of acrolein, contributing to the dysfunction of HDL in these patients.⁸

Neutrophil myeloperoxidase and increased oxidative stress, which are prevalent during inflammation and are associated with renal failure, oxidize LDL. During the acute phase response, HDL may lose its anti-inflammatory effect and actually become a pro-oxidant protein.⁹ This is in part due to a reduction in the content of antioxidant enzymes carried by HDL during the acute phase response, and in part because ApoA-I is replaced within HDL by an acute phase protein, serum amyloid A. Oxidized LDL is an important cardiovascular risk factor in its own right¹⁰ and is increased in dialysis patients. Normal HDL either prevents or delays LDL oxidation or reduces oxidized LDL, whereas HDL obtained from dialysis patients serves as a poor antioxidant, failing both to protect LDL from oxidative

injury and to reduce oxidized LDL.² Lipid hydroperoxides transfer from oxidized LDL to vascular endothelial cells, where they induce expression of MCP-1, an essential chemokine involved in monocyte traffic across endothelial and epithelial barriers that is responsible for monocyte chemotactic activity (Figure 1).

Vaziri *et al.*³ now report that addition of the ApoA-I mimetic peptide 4F to LDL obtained from dialysis patients reduces its capacity to increase monocyte chemotactic activity in vascular endothelial cells in culture. The term ‘ApoA-I mimetic protein’ is somewhat misleading, as the protein does not have any sequence homology to ApoA-I. The protein used, 4F, is a peptide 18 amino acids in length with four phenylalanine residues (single-letter amino acid code F, hence the name 4F) and is one of a group of peptides that have the capacity to form an amphipathic helix, similar to that formed by ApoA-I, mimicking many of the lipid-binding

properties of ApoA-I. ApoA-I is 243 amino acids in length and, like other apolipoproteins, is highly amphipathic, having both hydrophobic and hydrophilic domains. Vaziri *et al.*³ show that whereas HDL from normal control subjects was able to protect LDL from oxidation, HDL from dialysis patients was not. LDL from dialysis patients stimulated production of monocyte chemotactic activity by cultured aortic endothelial cells when compared with control LDL. The addition of 4F reduced this effect in the presence or absence of HDL from either dialysis patients or normal control subjects. The fact that 4F has an effect superimposed on normal HDL suggests that this may be a pharmacologic effect of the peptide and not be directly related to restoration of normal HDL function.

4F has been shown to be anti-atherosclerotic in experimental animals and also shifts ApoA-I from the α-migrating pool to the pre-β-migrating pool, potentially

facilitating its interaction with ABCG1 and thus allowing increased unloading of cholesterol from lipid-laden macrophages on arterial walls. In experimental models, oral administration of 4F increased PON1 activity in the pre- β -HDL fraction, a fraction not normally associated with PON1 activity, which might explain the protective effect of this peptide. 4F is less effective than native ApoA-I in activating LCAT, so this specific defect in HDL maturation observed in kidney failure is unlikely to be reversed by either 4F or other ApoA-I mimetic peptides. This agent, however, may serve as a pharmacologic tool to reverse abnormalities in HDL structure that accompany renal failure and may perhaps serve as a tool to repair vascular injury.

DISCLOSURE

The author declared no competing interests.

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It's not over till the last glomerulus forms

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The Brenner hypothesis postulated that low birth weight and decreased nephron number at birth are linked to chronic kidney disease and systemic hypertension in adulthood. To date, little is known about the effect of extrauterine growth retardation (EUGR) on adult kidney disease. Bacchetta *et al.* present novel data using inulin to show a decrease in renal function for premature children with EUGR. The role of protein nutrition and timing in nephrogenesis is discussed.

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Intrauterine growth retardation, influenced by the decreased supply of nutrients to the human fetus and its environment, with resulting low birth weight, was the basis of the Brenner hypothesis. This hypothesis, which states that low birth weight constitutes a risk factor for diseases in later life such as systemic arterial hypertension and chronic kidney disease, built on the Barker hypothesis, which first established a framework for the intrauterine origin of diseases suffered in adulthood. Since the late 1980s and early 1990s, when these theories were introduced, significant work has been generated to support an inversely related causal link between nephron endowment at birth and essential hypertension in adult humans, supporting the ideas of Barker and Brenner as more than hypotheses.¹

For babies born before 36 weeks of gestation, neonatal intensive care units are expected to replicate intrauterine development. However, many premature infants do not demonstrate the expected intrauterine growth at the time of discharge; this has resulted in a new term: extrauterine growth retardation (EUGR). Clark *et al.* define

EUGR as a growth value \leq 10th percentile of intrauterine growth expectation based on estimated postmenstrual age in premature neonates (23–34 weeks' estimated gestational age) at the time of discharge from the hospital.² To date, the notion of EUGR as a factor in the development of chronic kidney disease or adult-onset systemic arterial hypertension has not been fully developed. As nephrogenesis is not complete until 36 weeks of gestation, the potential effect of EUGR is particularly relevant in premature babies.³

In this regard, Bacchetta *et al.*⁴ (this issue) report on the renal function of premature babies (birth weight < 1000 g and/or < 30 weeks of gestation) in a single-center prospective cohort study. Although the authors address measures of blood pressure, kidney size, and tubular function, as others have done in the past, they demonstrate an association between EUGR and decreased glomerular filtration rate (GFR), but within the range of normal in childhood. They postulated that this moderate decrease in GFR may correspond to moderately reduced nephron number, which although asymptomatic in childhood, may have implications in adulthood. Bacchetta *et al.* also noted an association between decreased protein intake at 7 days of life and EUGR in premature babies. Their study is novel in that GFR was measured with the use of an exogenous marker, inulin, resulting in a more accurate assessment of GFR. When prior studies

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